Scientific Abstract

Colon cancer is a leading cause of cancer death in the United States and in Europe. At diagnosis, most patients have surgically resectable disease, but some individuals will develop a recurrence of the cancer despite appropriate surgical resection and local irradiation. The majority of patients who develop metastases will ultimately die of their disease (Moore and Haller, 1999). The 5-year survival rate for colorectal cancer patients treated with surgical resection is 90% for stage I, 70% for stage II, 50% for stage III and less than 5% for stage IV. For patients with metastatic cancer (Stage IV), gene therapy is a viable treatment option since the disease is invariably fatal.

A common site of metastasis of colon cancer is the liver. The liver receives blood from the hepatic artery and portal vein. The dominant blood supply of metastatic tumors is the arterial system. We have developed a matrix (collagen) - targeted retroviral vector bearing a dominant negative cyclin G1 construct (designated Mx-dnG1). This targeted vector accumulates at sites of exposed collagen caused by tumor invasion or tumor vessel formation, thus promoting tumor site-specific gene delivery. In a nude mouse model of liver metastasis, a significant reduction in the size of tumor foci in the liver was observed in Mx-dnG1 vector-treated mice compared to those of control vector- or PBS-treated animals ($p = 0.0002$).

These studies form the basis of the Phase I clinical trial for colorectal cancer metastatic to liver. The protocol is designed to assess the toxicity of the Mx-dnG1 retroviral vector, but will also assess potential tumor response. Only patients with unresectable colorectal carcinoma metastatic to liver who have failed all standard treatments are eligible to participate in the study. The specific objectives of the proposed study are:

1. To determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of the Mx-dnG1 retroviral vector administered as hepatic arterial infusion;
2. To evaluate the pharmacodynamics of the Mx-dnG1 retroviral vector when administered as hepatic arterial infusion;
3. To identify any objective tumor response to the Mx-dnG1 retroviral vector; and
4. To obtain preliminary data on molecular markers of tumor response.

The Mx-dnG1 vector will be infused into the hepatic artery over 6 hrs through a surgically placed Medtronic pump which may be placed at the time of liver biopsy. The Mx-dnG1 vector will be given daily for 5 days. The vector dose will be escalated according to protocol specifications. The primary endpoint of the study is clinical toxicity as defined by patient performance status, toxicity assessment score, and hematologic, liver and coagulation profiles. The secondary endpoint is a demonstrable decrease in tumor size as detected by abdominal CT Scan, MRI or PET Scan.